DoD Clinical Guidelines for Post-Smallpox Vaccine Associated Myopericarditis
Vaccine Healthcare Centers Network (VHCN)

Vaccine(s) administered in past 30 days

Clinical symptoms: Chest pain, shortness of breath, palpitations, syncope, dry cough, or any suspected cardiopulmonary symptom(s)

Initial Evaluation

History: Characterize symptoms[1]
Past medical history[2]
- Include detailed vaccination hx

Risk factors for cardiac symptoms[3]

Physical Examination[4]
Laboratory[5] (Troponin I/T, BNP, ESR, usCRP, CK-MB, **Viral surveillance**)
Diagnostics[6] (Electrocardiogram, Echocardiogram, CXR (PA/Lat), Pulmonary function testing, Imaging studies (Cardiac MRI with Gadolinium)

A. Symptoms only

A. Cardiology Consultation
- Document normal ECG, troponin, CK, CRP, other studies as indicated during acute symptoms[5,6]
- Consider non-cardiac etiology[7]

Therapeutic options[8]: NSAIDs +/- colchicine, other Rx
Management & Recovery[9]
- Activity based on exercise tolerance and clinical assessment
- 4 week clinical F/U visit, ECG, echocardiogram, and exercise stress test to clear for return to full duty
- For ongoing or persistent symptoms, refer to cardiology (stress test not recommended)

B. Symptoms + objective abnormality[11]

B. Cardiology Consultation
- Differential includes myo-pericarditis and acute coronary syndrome[5,6,7,11]

Special labs and diagnostics[5,6] as indicated

B1. Symptoms with objective ECG abnormality but without positive cardiac enzymes or LV dysfunction[11]

Therapeutic options[8]: NSAIDs +/- colchicine, other Rx
Management & Recovery[9]
- No strenuous activity for 6 weeks
- 6 week clinical F/U visit, ECG, echocardiogram, exercise stress test to clear for return to full duty; repeat abnormal studies
- For ongoing or persistent symptoms, refer to cardiology (stress test not recommended)

B2. Symptoms with positive cardiac enzymes, depressed LV function, and/or imaging c/w myocarditis[11]

Therapeutic options[8]: NSAIDs, other Rx
Management & Recovery[9]
- No strenuous activity for 6 weeks
- 6 week clinical F/U visit, ECG, echocardiogram, exercise stress test as clinically indicated; repeat abnormal studies (including cardiac enzymes)
- Activity as tolerated & deployment restriction for a minimum of 6 months
- Cardiology F/U at 6 months

B3. Includes B2 and any of the following: LVEF < 45%, sustained dysrhythmias, and/or hemodynamic instability[11]

- **Early Transfer** to Tertiary Care Center - consider myocardial Biopsy

Therapeutic options: see **Footnote 8**
Management & Recovery[9]
- No strenuous activity for 6 weeks
- Close clinical F/U as directed by cardiologists (echocardiogram, ECG, exercise stress test)
- Activity as tolerated & deployment restriction for a minimum of 6 months
- Cardiology F/U at 6 months for repeat evaluation (reassess deployability)

Refer **all** cases to VHC Network for clinical case review, entry into DoD Smallpox Vaccine Myopericarditis Registry, filing of VAERS report and natural history surveillance.[10] With referral include: Patient and provider contact information, Echocardiograms, ECG, cardiac isoenzyme results, & copies of pertinent records.

Consultation: Call the DoD Vaccine Clinical Call Center at 866-210-6469 to request VHC and/or military cardiology clinical consultation.

FOOTNOTES: The following guidance is for reference. Not every suggestion will be applicable to every patient. Recommendations are to be applied as diagnostic and therapeutic needs or questions arise and should be in conjunction with VHC staff consultation.

Footnote 1	**Characterize symptoms, including chest pain type**	Specify symptom location, character, onset, duration, intensity/severity, frequency, accompanying/associated symptoms, and alleviating/aggravating factors. All associated clinical symptoms should be detailed. Categorize patient's chest pain type if present (choose one): 1. Pericarditis chest pain: Chest pain that is typical and made worse by supine position, improved with leaning forward, pleuritic, constant a. Detailed history is critical to case definition of suspect pericarditis – see case definitions, page 5 2. Myocarditis chest pain: angina-like, diffuse; not necessarily positional or pleuritic 3. Atypical chest pain: Pain, pressure, or discomfort in the chest, neck, or arms not clearly exceptional or not otherwise consistent with pain or discomfort of myocardial ischemic origin. **Reference:** Box 10, Surveillance guidelines for smallpox vaccine (vaccinia) adverse reactions. (2006, February 3) *MMWR:Morbidity and Mortality Weekly Report, 55*(RR01);1-16. Retrieved from http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5501a1.htm
Footnote 2	**Assess past medical history**	Detailed review of all systems, with attention to the following disorders: ▪ Lung disease ▪ Gastrointestinal disease ▪ Vascular disease (e.g., stroke, transient ischemic attack, peripheral arterial disease) ▪ Musculoskeletal disorders (e.g., impingement syndrome, thoracic outlet syndrome) ▪ Vaccination history and adverse events (with specific lot number, if available) **Reference:** PMH study guide http://medinfo.ufl.edu/year1/bcs96/clist/history.html
Footnote 3	**Risk Factors for Cardiac Symptoms**	▪ Personal History of angina, myocardial infarction (MI), congestive heart failure (CHF), percutaneous coronary intervention (e.g., balloon angioplasty, stent, atherectomy), coronary artery bypass graft (CABG), catheterization with stenosis ≥ 50%. ▪ Age, sex, race/ethnicity (ethnicity: Hispanic or Latino, Not Hispanic or Latino; Race: American Indian or Alaska Native, Asian, Native Hawaiian or Other Pacific Islander, Black or African American, White)) ▪ Diabetes, hypertension, smoking, dyslipidemia, family history of CAD (especially prior to age 55), obesity, physical inactivity, stress, and excessive alcohol consumption. **Reference:** http://www.americanheart.org/presenter.jhtml?identifier=4726
Footnote 4	**Physical Examination**	Perform a focused PE to include: gender and race/ethnicity, vital signs, ht, wt, detailed exam to include vaccination site, cardiac (jugular venous pressure if able), pulmonary, peripheral edema and lymphadenopathy. Reference: http://meded.ucsd.edu/clinicalmed/introduction.htm
Footnote 5	**Laboratory studies**	Report normal range as defined by individual hospital laboratory standards. Record units and normal range for laboratory.
Laboratory studies: All patients		
	Complete blood count	CBC at presentation, to include differential, with emphasis on eosinophil and lymphocyte count should be noted.
	Cardiac enzymes	All Creatinine Kinase (CK), CK-MB, and troponin (I/T) values should be noted. For troponin data, document 99th percentile cut-off for testing system used as well as name of testing system if available.
	Inflammatory markers	All erythrocyte sed rate and C-reactive protein (CRP) (ultrasensitive, if available) values should be noted.
Laboratory studies as clinically indicated:		
	Immune complex screening	All Complement related assay studies (including C3, C4, CH50, C1q & C3D-binding assays) with values should be noted.
	Brain natriuretic peptide	Consider BNP if dyspnea is present.
	Viral surveillance	**Smallpox vaccine related myopericarditis is a diagnosis of exclusion.** No smallpox vaccine related cases have exhibited viral etiology to date**.** When considering other etiologies, viral surveillance is indicated.
	Serologies and PCR	Consider ID consultation; PCR for vaccinia if available (consult CDC/VHC). All **coxsackie A/B (enteroviruses), adenovirus, CMV, Parvovirus B19, influenza A/B, HHV-6, HSV-1, HIV, RSV**, dengue, echovirus, encephalomyelitis, Epstein-

		Barr, Lyme, rhabdovirus, varicella, variola, yellow fever, hepatitis A/B/C IgM, and core IgG values and titers during the evaluation should be noted; obtain specimens for convalescent titers at 4 week interval.
	Other Cultures	Consider ID consultation; all viral cultures (nasal wash, urine, feces) for adenovirus, influenza viruses, parvovirus B19 or enteroviruses should be noted.
	Autoimmunity screening	Note all ANA, Anti-DS DNA, ENA, and similar values during the evaluation. Consider additional special studies such as myocardial auto-antibodies. ***Consult VHC Network for current information.***
Footnote 6	**Diagnostics**	
Diagnostics: All patients		
	Electrocardiogram (ECG)	Note date, time, rate, rhythm, the presence of ectopy and abnormalities in waves, intervals and segments. Provide copies of relevant ECGs to patient and incorporate in record. **Typical ECG manifestations:** **Pericarditis:** Acute 1. Diffuse ST segment elevation, particularly leads I,II, III, aVF, aVL, and V5-V6 2. Diffuse PR segment depression 3. PR segment elevation in lead aVR Evolving 1. T-wave changes: notched, biphasic. Or low-voltage inversions. **Myocarditis:** 1. Diffuse T-wave inversions without ST segment abnormality 2. Incomplete atrioventricular conduction blocks (usually transient) 3. Intraventricular conduction blocks (usually transient) *When myocarditis and pericarditis occur together, ST segment abnormalities also may be evident. **Reference:** Demangone, D. (2006) ECG manifestations: Noncoronary heart disease. *Emergency Medicine Clinics of North America.* (24) pp.113-131.
	Chest X-ray	PA and Lateral
Other diagnostics as clinically indicated:		
	Echocardiogram	If only a range is estimated for ejection fraction (EF), note the midpoint of the range. For pericardial effusions, record estimate of size and/or clinical significance (small effusions may not be diagnostic).
	Pulmonary functions	With DLCO if indicated; diffusion capacity corrected for hemoglobin is a sensitive measure of pulmonary interstitial disease and increased risk for hypoxia with activity.
	Stress test	Indicate whether an exercise tolerance, stress-echocardiogram, or nuclear/pharmacological stress test was performed during the hospital stay and the result of the testing, if performed. Clinical correlation is recommended in the cases of a negative stress test result.
	Cardiac catheterization	If vessel occlusion identified, note the anatomical region affected and the degree of stenosis present.
	Holter & Event Monitor	Consider for dysrhythmia evaluation
	Imaging	Consider cardiac MRI with gadolinium (with T2W imaging and early/delayed enhancement) for cases with depressed EF and/or elevated Troponin as soon as feasible after onset of symptoms. **Reference:** Friedrich et al. Cardiovascular Magnetic Resonance in Myocarditis: A JACC White Paper. *JACC*, 2009; 53(17):1475-87.
	Myocardial Biopsy	Consider myocardial biopsy if heart failure is severe or worsening.
Footnote 7	**Differential Diagnosis**	Consider viral myocarditis, acute coronary syndrome (myocardial infarction), aortic dissection, pneumothorax, pulmonary embolism, musculoskeletal pain, esophageal disorder (gastroesophageal reflux, esophageal spasm), systemic autoimmune disease.
Footnote 8	**Therapeutic options**	***Consult VHC Network for current information.***
	Symptoms only (A) OR symptoms with objective findings, but with negative cardiac enzymes and no LV dysfunction (B1)	Non-steroidal anti-inflammatory therapy with or without colchicine (colchicine in addition to Conventional Therapy for acute pericarditis: Results of the colchicine for acute pericarditis (COPE) trial. Imazio M, et al. *Circulation* 2005; 112:2012-16.)

	Symptoms w/ positive cardiac enzymes or depressed LV function or imaging c/w myocarditis (B2)	Non-steroidal anti-inflammatory therapy. Other treatments to be considered in consultation with Cardiology and the VHCN to include corticosteroid treatment (after biopsy if possible). Consider biopsy for viral PCR, culture and assessment of inflammation (presence of eosinophils). Consider corticosteroids with evidence of eosinophilic inflammation and clinical deterioration.
	Progressive symptoms (LVEF < 45%, sustained dysrhythmias, hemodynamic instability) (B3)	▪ Conventional heart failure treatments (e.g., ACE inhibitors, nitrates, diuretics, select beta-blockers such as carvedilol or metoprolol succinate) ▪ Strongly consider early referral for myocardial biopsy to guide optimal treatment. ▪ Consider corticosteroids (preferably after biopsy) if no evidence of active infection and/or with evidence of eosinophils in inflammatory infiltrate. ▪ Consider Vaccinia Immune Globulin (VIG)/IVIG only with expert consultant case review via VHC Network.
Footnote 9	**Management and Recovery**	Whenever possible, standardized follow up should be coordinated with the Vaccine Healthcare Centers Network. **Reference** (Deployment Restriction): Maron et al. Task Force 4: HCM and other cardiomyopathies, mitral valve prolapse, myocarditis, and Marfan syndrome. *JACC*;45 (8):1340–5. http://content.onlinejacc.org/cgi/content/full/45/8/1340.
	Symptoms only (A) OR Symptoms with objective findings, but without positive cardiac enzymes or LV dysfunction (B1)	▪ Light physical activity at own pace for 4 weeks (A) ▪ No strenuous activity for 6 weeks (B1) ▪ Follow up in 4 weeks (A) to 6 weeks (B1) **Asymptomatic at follow-up** ▪ Repeat any previously abnormal studies ▪ Clinical evaluation to include stress test to assess exercise tolerance prior to clearance for return to duty ▪ Long-term follow-up will be completed by VHC Network **Symptomatic and/or persistent/abnormal findings at follow-up** ▪ Repeat any previously abnormal studies ▪ Clinical evaluation to include stress test (unless contraindicated) ▪ Repeat MRI if had previous enhancements or if symptomatic. Repeat at 12-18 months ▪ Consult cardiology for further recommendations ▪ Long-term follow-up will be completed by VHC Network

	Symptoms with positive cardiac enzymes or mild depressed LV function or imaging c/w myocarditis (B2) OR Progressive symptoms (LVEF < 45%, sustained dysrhythmias, hemodynamic instability) (B3)	▪ No strenuous activity for 6 weeks; deployment restriction for 6 months
		▪ Clinical evaluation at 6 weeks and 6-12 months
		Asymptomatic at follow-up
		▪ Repeat any previously abnormal studies at 6 weeks and 6-12 months
		▪ Stress test at 6 weeks to assess exercise tolerance for rehabilitation; repeat at 6-12 months to assess exercise tolerance prior to clearance for deployment
		▪ Long-term follow-up will be completed by VHC Network
		Symptomatic and/or persistent/abnormal findings at follow-up
		▪ Clinical evaluation to include enzymes, ultra sensitive CRP, ECG, ECHO, stress test (unless contraindicated)
		▪ Repeat MRI if had previous enhancements or if symptomatic. Repeat at 6 months to assess for clearance for deployment.
		▪ Clinical evaluation at 6 months to include repeat ECHO, stress test, and MRI
		  ▪ If normal and asymptomatic, clear for deployment
		  ▪ If normal and symptomatic, consult cardiology
		  ▪ If abnormal MRI with continued symptoms, not cleared for deployment
		▪ Continue cardiology follow-up at 6 -12 month intervals until asymptomatic
		▪ Long-term follow-up will be completed by VHC Network

Footnote 10	**Disability Assessment**	The majority of patients have recovered within 1 year. The natural history of this condition remains unknown. Careful functional assessment post-acute phase has not yielded definitive objective parameters. The long-term natural history of this condition (e.g., late onset arrhythmias, cardiomyopathy, recurrent myocarditis) has not been well defined. Development of new cardiac complications within 5 years following an episode of hypersensitivity myocarditis associated with immunization should be reported to the VHC Network clinical case management registry.

Footnote 11	**Case Definitions for Myocarditis and Pericarditis** *MMWR:Morbidity and Mortality Weekly Report* 2003;52:492-6, http://www.cdc.gov/mmwr/PDF/wk/mm5221.pdf *MMWR:Morbidity and Mortality Weekly Report*, 2006;55(RR01);1-16. http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5501a1.htm		
	Objective abnormalities		
Myo-carditis	**Suspect** (1) Symptoms (dyspnea, palpitations, or chest pain) (2) ECG abnormalities beyond normal variants, not documented previously (ST/T abnormality, paroxysmal supraventricular tachycardia, ventricular tachycardia, atrioventricular block, frequent atrial or ventricular ectopy) OR Focal or diffuse depressed LV function of uncertain age by an imaging study (3) Absence of evidence of any other likely cause	**Probable** (1) Meets symptom criteria for suspected myocarditis (2) In addition, meets one of the following: Elevated levels of cardiac enzymes (Creatine Kinase-MB fraction, Troponin T or Troponin I), OR new onset of depressed LV function by imaging, OR abnormal imaging consistent with myocarditis (MRI with gadolinium, gallium-67 scanning, anti-myosin antibody scanning)	**Confirmed** Histopathologic evidence of myocarditis by endomyocardial biopsy or on autopsy.
Peri-carditis	**Suspect** (1) Typical chest pain (made worse by supine position, improved with leaning forward, pleuritic, constant) (2) No evidence for alternative cause of such pain	**Probable** (1) Meets criteria for suspected pericarditis (2) Has one or more of the following: Pericardial rub on auscultation OR ECG with diffuse ST-segment elevations or PR depressions not previously documented OR echocardiogram revealing an abnormal pericardial effusion	**Confirmed** Histopathologic evidence of pericardial inflammation in pericardial tissue from surgery or autopsy